

Report of the Work under the Medical Research Fund done in the
Year 1913.

Dr. Fletcher McPhedran in the earlier part of the year was engaged in the study of the causation of Pernicious Anaemia. His results and conclusions were published in November in the Journal of Experimental Medicine, Vol. XVIII, No. 5, p. 527, under the title, - "On the Haemolytic Properties of Fatty Acids and their Relation to the Causation of Toxic Haemolysis and Pernicious Anaemia." Since that work was finished he has been engaged in investigations into functional defects of the kidneys in nephritis. Seeing that it is an important function of the kidney to assist in the maintenance of a normal reaction (hydrogen ion concentration) in the blood, to which it contributes by the secretion of acid urine; he has been investigating the hydrogen ion concentration in the urine under standard conditions in patients suffering from nephritis as compared with those whose kidneys are normal. The method he has employed was selected for its simplicity, because if the method was to be of common clinical value it must be easily carried out. By titrating urine to the phenolphthalein reaction with soda the amount of acid of the acid phosphate type is determined, as is known and as he has confirmed by means of the gas battery; and by titrating also with sulphuric acid to methyl orange the amount of base of the type of dibasic phosphate is; as he has similarly shown, determinable. By means of the two titrations therefore the ratio of acid phosphate to dibasic phosphate is established, and since the hydrogen ion concentration of solutions in various proportions of the two types of phosphates is known and can be graphically represented by a curve which he has obtained with the gas battery, agreeing closely with the curve given by Lörenzen, it is this way possible in a few minutes, by simple titration, to obtain the concentration of hydrogen ion in a specimen of urine. Using this method the diurnal variations in the urinary concentration of hydrogen ion on a standard diet is determined in specimens of urine collected every four hours and then the effect of the administration of 10 grams of acid, sodium phosphate at a certain hour is studied. Normal kidneys, as he has shown, excrete in the first and second four-hour periods after this a urine with a high concentration of hydrogen ion. He is now investigating the excretion under these conditions from nephritic kidneys in different stages or of different types, and before long will be able to report as to whether differences can be detected in the renal function in these different conditions and as to the diagnostic value, if any, of such differences.

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Dr. Imrie, who was appointed a junior Fellow in October, 1912, has been engaged in a study of the fatty changes in heart and kidneys that occur in various diseased conditions of these organs. It was shown a few years ago that in the liver accumulations of fat are characterized by the occurrence of fats composed of acids with a comparatively low iodine value and the evidence seems to indicate that fat is taken up normally by the liver and the acids there desaturated and since the evidence for this change occurring in other organs has hitherto been at any rate much less striking it has been questioned whether the more unsaturated acids found, for instance in the heart and kidneys have not been prepared in the liver and whether fatty changes in these organs would show anything of the character common in the liver. Dr. Imrie gave a preliminary report on his work at the meeting of the Canadian Medical Association at London last June, and has since then given a fuller account at the December meeting of the Society for Medical Research in Toronto. From a study of the organs from more than twenty human subjects he finds that the changes in the heart and kidney indicate that the same law applies to these organs as to the liver, that broadly speaking the more fat is present the lower the iodine value is; only the graphic presentation of the results seems to show that the decrease in the iodine value of the fatty acids from the heart and kidney corresponding to a given increase in the amount of fat in these organs is not as great as it is in the liver; but since the variations in the quantity of fat in these organs are far smaller than those to be observed in the liver, the curves run a very much shorter course and the relationship between amount and nature of the fatty acids is much less conspicuous than it is in the liver. The results and conclusions to be drawn from them will be published shortly in a paper which is now being prepared. Dr. Imrie has also studied these changes in animals in which they have been induced by the action of protagon. The results of these experiments will be published probably about the same time in a separate paper.

Dr. N. C. Sharpe, whose appointment dates from October, 1913, has been working on the qualitative changes in nitrogen excretions that accompany the febrile reaction of toxines (vaccines, tuberculin etc.) There has been a tendency in recent years to ascribe the increased nitrogen excretion in fevers generally, but especially in typhoid fever, simply to the low diet and the increased combustion necessary to account for increased heat production, and to deny any qualitative change in nitrogenous metabolism. And as a result of this the treatment of typhoid fever has been modified and a much more liberal diet prescribed. Without questioning the wisdom of this change in treatment, it is necessary to realize that there is a qualitative change in nitrogenous metabolism accompanying the reaction to typhoid vaccine as Dr. Sharpe has shown in experiments on himself. Whether the same change is to be observed in the febrile reaction to other vaccines, or toxines the experiments on which he is at present engaged will show. If it is, this fact will have an important bearing on the interpretation of the general reaction to infection - if it is not, entirely new facts in the specificity of the action of different toxines on metabolic processes must be brought into view.

Dr. Simon who was also appointed in October 1913, has worked on the estimation of fat in the blood for which at present no completely satisfactory method is known. It is too early yet to say whether he will be successful in working one out. He has lately been helping Dr. Sharpe in the experiments mentioned above, which involve a very large number of analyses and much labour. He also has some experiments in hand on the effect of light on haemato porphyrine injected into albino animals, which is known to cause dropsy and even rapid death.

The work carried on by Dr. R. G. Armour was under the following heads:-

1. Acquiring the necessary technical facility in the use of special methods of histological study of the central nervous system.
2. Special study by serial sections of a case of Hemiplegia which died in the wards of the General Hospital.
3. Study by serial sections of an obscure case of posterior degeneration of a cord, which died in the General Hospital. For comparison to these, a study of the cord of the cat, of which posterior roots of one side were cut and serial sections cut and stained by various histological methods.
4. Study of the brain in general paralysis of the insane and of the cords in tabes by the Levaditi method and modification of the same in an attempt to localize by spirochaete in definite areas.
5. Histological study of several brain tumors.

Dr. Caulfield's researches have been chiefly devoted to Tuberculosis; and when other infections have been taken up, it has been for the purpose of helping to elucidate questions in the main work. As considerable equipment had to be installed, work was not begun until the end of March 1913.

The end in view has been to demonstrate, if possible, under what biological conditions infection to tuberculosis takes place, if possible those biological conditions that are essential to the patient's recovery. Provided these facts could be satisfactorily obtained, it was then proposed to attempt to reproduce these conditions experimentally in animals with the ultimate hope of using the Sera (or cell emulsion) as a specific means of curing, or aiding the recovery in human subjects.

Owing to the peculiar character of Tuberculosis, in that there are many subjects who have recovered naturally from this disease without the knowledge that they had ever contracted this infection, it has been found necessary to carry on extensive observations upon cases of doubtful diagnosis, cases who have been very intimately exposed, and those in whom there would be no suspicion of Tuberculosis, as well as the definitely tuberculous.

To make the biological data of any value whatever, it was also necessary to realize an organization so that accurate clinical notes could be made of the subjects under investigation, and repeated at the time of further biological data.

Over 200 cases have been observed in this manner, and of these, over one half have had biological and clinical data repeatedly recorded. The biological data consists in recording the tuberculin sensitiveness, and in demonstrating certain of the so called immune substances in the blood, together with a particular body designated by Dr. Caulfield as "Inhibitin".

The results so far obtained might be summarized as follows:-

In definite tuberculosis cases repeated tests give different types of biological curves which correspond, and in some cases precede the variations in the general clinical condition of the patient. This is often extremely remarkable, but on occasions the relation is not clear cut. Such a result is, however, perfectly satisfactory, because it is often extremely difficult to determine that the apparently unfavourable welfare of the patient is not due to some other factor than activity of the Tuberculosis.

Observations upon cases which have been very intimately exposed to the disease, and which have shown no clinical evidence after a considerable period of time, that they had contracted it, support the theory that a slight but transient infection has followed the exposure, but that the subject made his own recovery. In these cases it seems necessary that these subjects develop the substance "Inhibitin" and one of two other biological conditions. It is difficult to obtain examples of this class and further, there seem to be differences depending on how long the subject has been exposed. For example, one subject may be a husband who has slept for years with a badly infected wife, and the other a student who was exposed to a bed-fellow student who had probably had tuberculosis for only a very few months.

The practical value of this research on persons exposed, is illustrated by the following:-

A young man, after two months' engagement, learnt that his fiancee was tuberculous. A few days after this, he showed that he had the two chief immune substances in small amounts. Under favourable circumstances and after three months, during which time he did not see his fiancee, he had both these substances increased to a very high degree. It was then possible to tell him that he had been infected, and had made a natural recovery, and with care need not fear the results of his exposure.

The results of the observations upon cases where the diagnosis of tuberculosis could not definitely be made or excluded, should, of course, be very valuable, but here the interpretation becomes the most difficult. The only way in which these can be brought to a conclusion is by repeated observations. Many of these have on repeated biological examinations, shown no evidence of the specific immune bodies while at the same time the patients has lost the complaints which made an exclusion of tuberculosis impossible, because no other adequate cause could be found. Here the diagnosis is clear, i.e., there never was any tuberculous infection. Other cases have shown, as in the instances of the exposed case cited above, an increase of the specific immune bodies with more or less loss of the complaints. In these cases as there is now no doubt of the tuberculosis, it merely becomes a question regarding how much treatment should the patient receive to enable him to certainly recover from the disease. There are, however, a large number of the doubtful diagnosis cases, where the complaints remain about the same, and where the immune substances are so slight, or vary so slightly, that this might possibly be due to technical errors in performing the tests. Sufficient observation both clinical and biological, and time alone can decide this. It is felt however, that during such time as is needed on these latter cases, that the disease even if present, is not making dangerous headway.

The purpose of carrying out the observations on apparently normal subjects is, because if a sufficient number are kept under observation for a sufficient period of time, some of these will contract the disease, and depending on their resistance will throw it off in a longer or shorter period of time - or the disease will make sufficient headway, that it will become recognizable by ordinary methods. In this way, it is hoped that observations may be obtained showing the

biological conditions under which infection takes place naturally, and those conditions under which the disease is thrown off, or makes headway against the subject. Three of the cases out of a total of twenty six are showing variations that suggest very strongly that they have lately injected Tubercle B.

As a preliminary to possible work with animals, Dr. Caulfield has made observations upon the smaller type of laboratory animals, before, and after experimental inoculation of tubercle Bacilli, and their products. Here it was found that the biological conditions resulting was usually quite different from that obtained in humans, but then, there is the differences that these animals are usually more susceptible to tuberculosis than man. Tests were made upon twenty three cows at the Ontario Agricultural College at Guelph, and at Erindale Farm. From these it was found, that apparently identical conditions were obtained, in cows, as in man. For the purposes of complete comparison it was found that in neither place was it satisfactory to have to rely upon the convenience and kindness of others to perform carefully the tuberculin tests, and keep a record of the cows health. Besides this, there was the great disadvantage of time lost by frequent trips to Guelph, which offered more satisfactory conditions than Erindale.

It is felt by Dr. Caulfield that the biological variations found during the activity of the disease together with the data obtained among those in whom it can reasonably be concluded, that the disease has spontaneously subsided, show that he has now demonstrated in part at least, the specific biological states arising during infection and recovery; that although the results of the tests may in different cases be of great value for the diagnosis and treatment of cases, the routine carrying on of this work should not be considered as research. From the point of view of research, the work should be concluded, as soon as sufficient time has elapsed, especially in certain of the cases of doubtful diagnosis.

The logical advancement of the work, is to arrange for experimental work in cattle. Provided the proper biological conditions can be produced ; experimentally - which the observations already give promise of - the exhibition of a specific serum from such animals would be based upon a long series of newly elicited facts leading up to such an attempt. It would not be the result of theory alone, which has too frequently been the sole basis for the use of many of the remedies which have in the past disappointed the hopes raised by the theories of the investigator.

It is proposed to present certain of the results of the research, before the Meeting of the Association of American Pathologists and Bacteriologists at Toronto, and the Association for Prevention and Cure of Tuberculosis at Washington. The results, as soon as completed, will be published in the Autumn of this year.

The Medical Clinic of the Out-Patients' Department of the Toronto General Hospital has been established by the Board of Trustees on such a basis that the Chief in charge is given a very free hand. The Superintendent of the Hospital with the Professor of Medicine retain advisory rights and the power of veto. The only fixed requirements are that the patients shall receive thorough investigation and prompt aid, that complete records shall be kept of the Patients' progress and that the fifth year students in medicine shall receive direction in the investigation of cases and the treatment of patients as should be carried out in private practice.

The details of the organization and the recommendation for appointment to the staff is left to the Chief, Dr. William Goldie.

These powers of the Chief, the active aid of the administration, the co-operation of the Social Service and the sympathy of the members of the Laboratories of the Medical Faculty, make it possible to use the increasing number of patients attending the Clinics for the investigation of disease.

The nature of the work at such a Clinic makes the character of the investigations differ from that which can be undertaken in the wards of the hospital. The intermittent and irregular attendance of the patients, and the need of caring for the routine work during such attendance, precludes all such investigations that have to do with metabolism and confines the research to the interpretation of symptoms, the earliest signs and symptoms of disease, the surrounding causes for the origin and spread of disease, the hereditary faults, the application of diagnostic and control tests and the best means of control and treatment.

The scope is great and offers many opportunities for those clinical investigations which, consuming so much time and requiring such persistence before definite results can be obtained, are almost impossible to carry out under the conditions which have existed.

To overcome the natural difficulties of the situation the organization of the Clinic has for its object, the concentration of the energies of the staff upon the investigation of special objects.

For this purpose those members interested in a particular disease or disease group, together with members to help in the routine work, have been formed into units attending twice a week, and patients suffering from these diseases are referred to those days for special attention and investigation.

At present there are six such units consisting of from three to four members. Three form sub-clinics in Tuberculosis, Diseases of the Skin and Diseases of the Nervous System and the other three from the General Medical Clinic, having allotted the broad subjects of Heart Affections and Chronic Infections; Gastro-Intestinal.

Diseases; and Anaemias and Habitual Constipation.

These subjects for the General Medical Clinic were purposely made broad, for there were no data at hand of the classes of disease or the numbers of each that would be met with in dispensary work in this city. Experience of six months will determine what subjects can be profitably investigated, but it has already determined that occupational diseases must come under the control of one or more units and that a control and treatment clinic for syphilis must be formed, and also it has led to the allotment of special subjects to certain members.

The Staff has been selected with the object of having laboratory and clinical workers engage in research or some subject of common interest and thus obtain more complete and valuable records. The effect of the union on a common object shows not only in the records but upon the members of the unit, in that there is an increased enthusiasm and thoroughness in the work and a better realization of the need of co-operation. This is reflected in the desire of the members doing routine work to engage in special investigation.

